

Gentalen et al.
Application No.: 09/930,536
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PATENT

Attached hereto is a marked-up version of the changes made to the specification by the amendment. the attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (650) 326-2400
Fax: (650) 326-2422
JOL:adm
PA 3176657 v1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at page 9, line 7 has been amended as follows:

Fig. 4. Fluorescence images of cooperative vs. non-cooperative hybridization to paired probe arrays. The design of the array is shown in Fig. 3. Unambiguous hybridization to the double perfect match probe pair is shown for four different linked sequence pairs (10g-27c, 10c-27t, 10c-27g, and 10g-27t from top of left hand column)(SEQ ID NO:1). Hybridization images of the corresponding unlinked targets are shown in the adjacent right hand column.

The paragraph beginning at page 9, line 16 has been amended as follows:

Fig. 4.5 50:50 mixtures of (10c-27t and 10g-27c)(SEQ ID NO:1) and (10g-27t and 10c-27c)(SEQ ID NO:1) are shown in the two panels of the left hand column. Although the two experiments have targets that are identical in sequence composition, the pairing is different. This is clearly detected in the experiment, which allows the pairings (linkages) to be determined in each case. The bottom panel in the right hand column shows a hybridization image of (10c, 10g, 27c, and 27t). The sequence composition is identical to the two lower panels of the left hand column. However, in this case the individual targets are unlinked, and hence no cooperative effect is observed.

The paragraph beginning at page 30, line 33 has been amended as follows:

Labeled DNA Targets. DNA oligonucleotides bearing a 5' terminal fluorescein label were synthesized on solid supports using standard phosphoramidite chemistry. Oligonucleotides 10c-27c, 10g-27t, 10c-27t, and 10g-27c are based on the sequence 5'-Fcc act cac gNg agc tct cca tgc att Ngg tat ttt cgt ctg gga ggt atg cac gcg ata gca, (SEQ ID NO:1), where F denotes fluorescein. The letter N indicates positions 10 and 27. The base at these positions is indicated in the name of each oligonucleotide. Likewise,

oligonucleotides 10c and 10g are based on the sequence 5'Fct cac gNg agc tct c, (SEQ ID NO:2), and 27c and 27t are based on 5'F tgc att Ngg tat ttt (SEQ ID NO:3). The 10c, 10g, 27c, and 27t sequences were derived from the position 10 and 27 double variants listed above. In addition to the oligonucleotide targets, human mitochondrial DNAs of 160 bases and 2.5 kb were prepared using single-stranded asymmetric PCR. These DNAs were amplified from samples previously sequenced on an ABI 373A DNA Sequencer. Labeling was by incorporation of biotin-16-dUTP during PCR. Two 2.5 kb amplicons were prepared, differing at three positions. Amplicon 1 had the sequence 93c-1438c-2131a. Amplicon 2 had the sequence 93t-1438t-2131g.

The paragraph beginning at page 31, line 24 has been amended as follows:

A 4 x 4 array was synthesized, in which each 400 μ m x 400 μ m site contained a mixture of two different 9-mer probe sequences, Probe 1 (3'-gtgcN1ctcg-5')(SEQ ID NO:4) and Probe 2 (3'-gtaaN2ccat-5')(SEQ ID NO:5). To demonstrate that any cooperative effect was sequence-specific, we designed the array to include four variants of each of the probes, in which the central base of Probe 1 and Probe 2 was substituted with A, C, G, or T. The resulting array contained 16 sites. Each site contains a different combination of N1 and N2 for the two probes. In this way all sixteen mixtures of Probe 1-N1 and Probe 2-N2 were synthesized (Fig. 3).